Conclusion: Pemetrexed 900 mg/m^2 did not improve survival, progression-free survival or tumor response over pemetrexed 500 mg/m^2 for patients with platinum-pretreated advanced NSCLC patients. Certain toxicities and clinical sequelae were more frequent in the high dose group. Pemetrexed 500 mg/m^2 iv q3week should be considered the standard dose for second-line treatment of NSCLC.

Maximum CTC Toxicity, Grade 3/4, Occurring in > 5% Patients in Either Arm, Regardless of Causality	P 500 N=290	P 900 N=240*
Neutropenia	3.4	7.9
Anemia	4.5	5.8
Thrombocytopenia	2.8	5.4
Fatigue	7.9	11.3
Dyspnea	5.2	5.4
Infection without neutropenia	5.2	6.3

*Safety data for the 51 pts who switched from P 900 to P 500 are not shown here.

A3-04 **Cytotoxic Chemotherapy I, Mon, 13:45 - 15:30**

A phase III study by the Norwegian Lung Cancer Group: Pemetrexed + carboplatin vs. gemcitabine + carboplatin as first-line chemotherapy in stage IIIB/IV non-small cell lung cancer

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Background: Pemetrexed has shown activity in non-small cell lung cancer (NSCLC), both as single drug and in combination with platinums. A prospective, randomized, multicentre study was conducted to compare pemetrexed + carboplatin (PC) with a standard regimen, gemcitabine + carboplatin (GC).

Methods: Chemonaive patients with verified NSCLC, stage IIIB (ineligible for curative radiotherapy) or stage IV, WHO performance status (PS) 0-2, adequate hematology and calculated creatinine-clearance ≥ 45 ml/min were eligible. All patients were supplemented with folic acid 0.4 mg OD and vitamin B12 1 mg IM every 9 weeks, from ≥ 5 days before and through the treatment period. Patients were randomized to receive either pemetrexed 500 mg/m^2 + carboplatin AUC=5 (Calvert's formula) day 1 or gemcitabine 1000 mg/m^2 day 1 & 8 + carboplatin AUC=5 (Calvert's formula) day 1. Maximum 4 courses were given every 3 weeks. Primary endpoints were defined as global health, nausea/vomiting, dyspnea and fatigue measured by the EORTC QLQ-C30 and LC13 before every cycle and until 11 weeks after chemotherapy. Secondary endpoints were overall survival (OS) and toxicity measured by the CTCAE v3.0. Stratification was done for age (<75 vs ≥75 years), stage (IIIB vs IV) and PS (0-1 vs 2). 190 evaluable patients in each arm were required to detect a 15 % improvement on predefined QoL parameters with an α of 0.05 and β of 0.80. A loss to follow up of maximum 15 % was expected.

Results: 446 patients were enrolled from Apr 05 - Jul 06. The two arms were well balanced with respect to age, gender, stage, PS and histological classification. 423 patients were eligible for the primary QoL-analysis and analyses on toxicity (patients who received ≥1 cycle of chemotherapy). There were no statistical significant differences in mean score of the primary endpoints between the treatment arms. No difference in grade 3-4 anemia was observed (13 % vs. 12 %). Significantly more patients in the GC arm experienced grade 3-4 thrombocytopenia (57 % vs. 24 %, p<.001), leucopenia (46 % vs. 22 %, p<.001) and granulocytopenia (51 % vs 39 %, p=.027). More patients in the GC arm received transfusion of platelets (9 % vs. 3 %, p=.007). No difference in the frequency of neutropenic fever was recorded. The final OS analyses will be presented at the IASLC World Conference.

Conclusions: No differences were detected between the two arms with respect to the primary QoL outcome. However, patients in the PC arm experienced significantly less toxicity with respect to leucopenia, granulocytopenia and thrombocytopenia.

A3-05 **Cytotoxic Chemotherapy I, Mon, 13:45 - 15:30**

Phase III study of vinflunine versus docetaxel in patients (pts) with advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with a platinum containing regimen

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Background: Vinflunine is a novel microtubule inhibitor obtained by semi-synthesis using superacidic chemistry to selectively modify the catharanthine moiety of Vinca alkaloid with clinical activity in NSCLC (J. Bennouna, BJC, 2006). Single-agent efficacy and safety of VFL and docetaxel (DTX) were compared in second line NSCLC.

Methods: Open-label, multi-centre, randomised, phase III study in platinum pre-treated advanced/metastatic NSCLC pts. At least 275 pts were to be randomised by arm to receive VFL (320mg/m^2, 20-min IV infusion) or DTX (75mg/m^2, 1-hour IV infusion with dexamethasone over 3 days) every 3 weeks. The primary objective was to compare progression free survival (PFS), with a non-inferiority analysis based on a 10% difference (types I and II error rates: 5%, 20%), response and safety were assessed according RECIST and NCI CTC (version 2.0) respectively. Patient's benefit was also evaluated. From 06/03 to 03/05, 551 pts were randomised (VFL: 274; DTX: 277) and 547 treated (411 men, 136 women; median age 61 years [range 22-83]; ECOG PS 0-1: 89%; metastatic: 90%). All pts were platinum pre-treated, in combination with a vinca alkaloid (22%), paclitaxel (21%), or gemcitabine (48%). A total of 950 [1-20] and 1025 [1-18] cycles were given with VFL and DTX respectively. Grade 3/4 toxicities: neutropenia (33% v 30%), anaemia (8% v 3%), thrombocytopenia (2% v <1%), febrile neutropenia (3% v 5%), fatigue (11% v 6%), vomiting (2% v 1%), abdominal pain (4% v <1%), constipation (7% v <1%) resulting in low toxicity in both arms. Alopecia (20% v 35%), nail disorders (1% v 6%), injection site reaction (25% v 1%), peripheral neuropathy (11% v 15%), diarrhoea (6% v 12%) were observed. Efficacy: All efficacy end-

points were similar: median PFS (2.3 v 2.3 months, hazard ratio: 1.004 [0.841-1.199]), response rate (4.4% v 5.5%), stable disease (36.0% v 39.6%), median overall survival (6.7 v 7.2 months, hazard ratio: 0.973 [0.805-1.176]). Clinical benefit was a composite endpoint based on PS, weight, PPI, analgesic consumption, dyspnoea and cough; the primary endpoint of clinical benefit analysis was the rate of clinical benefit responders, defined as those patients who demonstrated improvement in at least one of these parameters, without deterioration in any other parameter, and confirmed once at least three weeks later. No significant difference was observed in the rate of clinical benefit between the vinflunine arm (31 responders, 13.1%, 95% CI 9.1-18.0) and the docetaxel arm (39 responders, 15.5%, 95% CI 11.3-20.6: c^2, p=0.4389).

Conclusion: Vinflunine 320 mg/m^2 every 3 weeks was found to be similar in terms of efficacy to docetaxel 75 mg/m^2 every 3 weeks in patients previously treated with a platinum-containing regimen for advanced NSCLC patients. Clinical benefit was also comparable for the two study treatments. Low, manageable but different toxicity profiles were observed in either arm allowing a good median relative dose intensity > 98%. Therefore, vinflunine offers a new and useful alternative for patients suffering from advanced NSCLC in second line setting.

A3-06 **Cytotoxic Chemotherapy I, Mon, 13:45 - 15:30**

Triplets versus doublets with or without cisplatin in the first-line treatment of stage IIIB-IV non-small cell lung cancer (NSCLC) patients: preliminary results of a multicenter randomized factorial study

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Background: Platinum-based chemotherapy doublets represent the standard first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), although toxicity is common. Several randomized trials trying to assess whether non-platinum combinations were as effective as platinum-based ones yielded conflicting results. Moreover, another not completely solved question is whether triplet regimens could be more effective than chemotherapy doublets. This 2 x 2 factorial trial aimed at answering both questions: (1) the role of replacing cisplatin (P) with vinorelbine (N), (2) the role of adding a third agent, ifosfamide (I), in a chemotherapy doublet with gemcitabine (G). Primary endpoint was overall survival (OS). Secondary endpoints were response rate (RR), progression-free survival (PFS) and toxicity.

Methods: Patients with stage IIIB or IV NSCLC were randomly assigned to one of four first-line regimens: gemcitabine 1250 mg/m^2 on days 1, 8 plus cisplatin 80 mg/m^2 on day 1 (GP); gemcitabine 1250 mg/m^2 on days 1, 8 plus vinorelbine 25 mg/m^2 on days 1, 8 (GN); gemcitabine 1000 mg/m^2 on days 1, 8 plus ifosfamide 2 g/m^2 on day 1 plus cisplatin 80 mg/m^2 on day 1 (GIP); gemcitabine 1000 mg/m^2 on days 1, 8 plus vinorelbine 25 mg/m^2 on days 1, 8 plus ifosfamide 3 g/m^2 on day 1 (GIN). Treatments were repeated every 3 weeks for a maximum of 6 cycles. Considering the 2 x 2 trial design, two comparisons have been performed: (1) N-containing vs P-containing regimens [GN and GIN vs GP and GIP] and (2) I-triplets vs I-non containing doublets [GIN and GIP vs GN and GP].

Results: From 10/2001 to 07/2006, a total of 433 patients were randomized. The patients characteristics were as follows: 72% males, with median age of 63 years (range of 29-79), 40% adenocarcinomas, 71% stage IV and 53% with ECOG performance status of 0. About the comparison (1), RR was 25.6 vs 36.3% (p = 0.032), PFS 5.0 vs 6.5 months (p = 0.239) and OS 11.1 vs 9.8 months [Hazard Ratio (HR) = 1.04; 95% C.I.: 0.82-1.33; p = 0.719] for N-containing vs P-containing regimens, respectively. About the comparison (2), RR was 29.1 vs 32.8% (p = 0.471), PFS 6.5 vs 5.5 months (p = 0.519) and OS 10.8 vs 9.8 months (HR = 0.95; 95% C.I.: 0.74-1.21; p = 0.705) for I-triplets vs I-non containing doublets, respectively. Grade 3-4 anaemia, leucopenia and thrombocytopenia were significantly more frequent in P-containing regimens; only grade 3-4 leucopenia was more common in I-triplets. Concerning non-haematological toxicity, only grade 3-4 nausea-vomiting was significantly increased in P-containing regimens; no other statistically significant difference in toxicity was observed.

Conclusions: Results of this unplanned preliminary analysis indicate that replacing P with N or the addiction of I to a chemotherapy doublet regimen did not improve OS in the treatment of stage IIIB-IV NSCLC patients. However, P-containing regimens showed a statistically significant advantage in RR over P-free chemotherapy.

A3-07 **Cytotoxic Chemotherapy I, Mon, 13:45 - 15:30**

A prospective randomized multi-center trial of three chemotherapy regimens in Korean patients with advanced non-small cell lung cancer - an interim analysis of Korean Association for The Study of Lung Cancer (KASLC)-0301 trial

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Background: Chemotherapeutic response rate would be different by the ethnic background. This is a randomized prospective trial of three cisplatin-based chemotherapeutic regimens in Korean patients with advanced non-small-cell lung cancer.

Methods: A total of 333 patients with advanced non-small cell lung cancer were randomly assigned to one of the three regimens of 3-weekly cycle: cisplatin of 60 mg/m^2 on day 1 with docetaxel of 75mg/m^2 (DP) or paclitaxel of 130 mg/m^2 (TP) on day 1, or gemcitabine of 1200mg/m^2 on day 1 and 8 (GP). After 2~3 cycles of chemotherapy, non-responding patients were crossly assigned to the second-line monotherapy of either docetaxel or gemcitabine.

Results: There was no significant difference in sex, stage, and performance status (PS) score, number of cycles and delivered dose intensity between the 3 groups. Three fourths of the patients had stage IV disease and one fourth showed ECOG PS score of 2. Mean cycle of the first-line chemotherapy was 3.4, and the relative dose intensity was 97%. The overall response rate was 41.8%, with a median survival of 328 days (95% CI: 271~385) and median progression free survival of 139 days (95% CI: 111~167 days). The response rate and progression free survival did not differ among the 3 groups. The first-line treatment